REMARKS

Claims 1-15, 24-37, and 41 are pending. No claim is allowed.

Applicants note that a copy of the Kolterman reference is included herein, and again respectfully request the examiner's consideration of this reference. *See* Exhibit 5.

Rejection Under 35 U.S.C. § 103 (a)

Claims 1-14, 24-36 and 41 remain rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Karpe et al. (Metabolism 48:301-07 (1999)) in view of Beeley et al. (WO 98/30231) and Beers et al. (the Merck Manual, 1999, 17th edition, pages 200 and 2550) for reasons of record. Claims 15 and 37 remain rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Karpe, Beeley, and Beers further in view of Wagle et al. (U.S. Patent No. 6,326,396). Briefly, the Examiner alleges that Karpe discloses that the postprandial elevation of plasma triglycerides is more closely linked to coronary heart disease than fasting triglyceride levels and is associated with signs of early atherosclerosis in healthy men. The Examiner acknowledges that Karpe fails to teach a method for lowering triglycerides with an exendin. According to the Examiner, Beeley teaches the use of an exendin or an agonist thereof to lower plasma lipids. The Examiner also asserts that Beers discloses that triglycerides are triglyceride is a major plasma lipid. The Examiner concludes that Beeleys' plasma lipids would inevitably include triglycerides, and therefore, it would be obvious to treat a patient having elevated triglycerides. *See* Final Office Action dated June 6, 2005 at page 3, lines 23-25. Applicants traverse this rejection.

Applicants respectfully submit that the cited combination of references fails to render the claimed methods *prima facie* obvious for reasons already of record as well as those discussed herein.

First, the obviousness rejection appears to be based on the premise that lowering plasma lipids necessarily lowers triglycerides. A teaching of lowering plasma lipids without more fails to teach or suggest the lowering of a particular subclass of lipids as individual classes of plasma lipids are differentially regulated. The present claims relate to the lowering of triglyceride levels

by administering an exendin or an exendin agonist to a patient identified as having elevated postprandial triglyceride levels. Triglycerides represent one of several classes of plasma lipids. Others include cholesterol-containing lipids such as high-density lipoproteins (HDL) and low-density lipoproteins (LDL). These classes of lipoproteins are differentially regulated. In other words, the lowering of one class, *e.g.,* LDL, does not necessarily result in a reduction in another class, *e.g.*, plasma triglycerides. A number of therapeutic agents result in the differential reduction of one class of plasma lipids, but not another. For example, a combination of enalapril and valsartan resulted in a reduction in total cholesterol and LDL, an increase in HDL, and no change in triglyceride levels in patients with diabetes and hypertension. *See e.g.,* Exhibit 1 at Abstract. In another study, hormonal replacement resulted in significant lowering of total cholesterol, HDL, and LDL without any significant changes in triglyceride levels. *See e.g.,* Exhibit 2 at Abstract. Even in patients with hyperlipidemia, lipid-lowering drugs differentially affect lipid profiles. *See e.g.*, Exhibit 3 at Abstract (discussing the failure of pravastatin, a HMG-CoA reductase inhibitor, to lower plasma triglyceride levels while lowering LDL levels). Such studies demonstrate that plasma lipids are differentially regulated and differentially affected by lipid-lowering agents.

Second, an obviousness rejection cannot be supported by the assertion that a reduction in food intake results in a lowering of triglyceride levels. A reduction of food intake does not uniformly lower triglycerides levels. In fact, a recent review indicates that a reduction of food intake results in unchanged triglyceride levels while other plasma lipids levels can be lower. *See* Exhibit 4. In this article, the authors examined the outcome of diet (*i.e.*, reduction of food intake) in 1745 patients on 91 different diets on plasma triglyceride levels. *See id.* at Table 5 and page 1845. In patients with lower caloric intake (*i.e.,* lower carbohydrate diet), there was no change in plasma lipid levels (including plasma triglycerides). In patients with higher carbohydrate diets, total cholesterol levels were reduced, but other plasma lipids (including triglycerides) were unchanged. *See id.* In sum, plasma triglycerides were not reduced using any number of methods used to reduce food intake. Such objective data demonstrates that a teaching of reducing food intake does not inherently result in a lowering of plasma triglycerides.

In view of the above, Applicants respectfully submit that Karpe in combination with Beeley, Beers, and Wagle fail to render the claimed methods *prima facie* obvious in view of the absence of any teaching or suggesting of using exendin or its agonists to reduce plasma triglycerides in patients with elevated postprandial triglyceride levels.

The combination of cited references fails to teach or suggest each and every element of the claimed methods. Karpe merely discloses a correlation between elevated triglycerides and CHD. As acknowledged by the Examiner, Karpe lacks any teaching or suggestion of lowering triglycerides in patients with elevated postprandial triglyceride levels using an exendin or an exendin agonist alone or in combination with a statin. The remaining cited references fail to cure these deficiencies. Beeley is completely silent with regards to lowering plasma triglycerides. Beeley discloses a method of reduction of food intake using an exendin or an exendin agonist – a teaching that fails to inherently or expressly disclose a lowering of plasma triglycerides. As discussed above, the reduction of food intake fails to inherently result in lowering of plasma triglycerides and the distinct classes of plasma lipids are differentially regulated. Therefore, without more, Beeley fails to cure the deficiencies in Karpe. Beers' identification of triglycerides as a class of plasma lipids fails to extend the teachings of Karpe and Beeley to the claimed methods. Wagle's disclosure regarding statins also fails to correct the deficiencies in the cited combination. Because the cited combination of references fails to teach or suggest each and every element of the claimed methods, they fail to render the claims *prima facie* obvious.

Moreover, in the absence of a teaching or suggestion of each and every element of the claimed methods, the cited combination can provide neither motivation nor a reasonable expectation of success for modifying the teaching of Karpe in view of Beeley, Beers, and Wagle to result in the claimed methods.

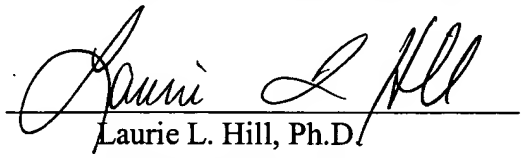
For at least these reasons, Applicants respectfully request the withdrawal of the obviousness rejection.

CONCLUSION

No fees are believed due for this submission. However, if a fee is due, the Commissioner is hereby authorized to charge payment of any fees associated with this communication, to Applicant's Deposit Account No. 010535. Additionally, the Commissioner is hereby authorized to charge payment or credit overpayment of any fees during the pendency of this application to Applicant's Deposit Account No. 010535.

Respectfully submitted,
AMYLIN PHARMACEUTICALS, INC.

Dated: December 2, 2005

By: 
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Also included herewith are the following Exhibits:

Exhibit 1: Gaudio et al., *J. Cardiovasc. Pharmacol.* 45:362-66 (2005).

Exhibit 2: Ödmark et al., *Maturitas* 48:137-46 (2004).

Exhibit 3: Saklamaz et al., *Metabolism Clin. Exp.* 54:677-81 (2005).

Exhibit 4: Bravata et al., *JAMA* 289:1837-50 (2003).

Exhibit 5: Kolterman